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Review article:

PARTICLES FROM PREFORMED POLYMERS AS CARRIERS FOR DRUG DELIVERY

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ABSTRACT

Biodegradable and biocompatible polymers are widely used for the encapsulation of drug molecules. Various particulate carriers with different sizes and characteristics have been prepared by miscellaneous techniques. In this review, we reported the commonly used preformed polymer based techniques for the preparation of micro and nano-structured materials intended for drug encapsulation. A description of polymer-solvent interaction was provided. The most widely used polymers were reported and described and their related research studies were mentioned. Moreover, principles of each technique and its crucial operating conditions were described and discussed. Recent applications of all the reported techniques in drug delivery were also reviewed.

Keywords: Drug delivery, particles, polymer, encapsulation, carriers, operating conditions

INTRODUCTION

Particulate carriers have gained tremendous interest during the last decades which permitted to deliver many hydrophilic and hydrophobic molecules. Obtained particles present small size which facilitates their absorption. These drug delivery systems protect active pharmaceutical ingredients from degradation, enhance biopharmaceutical properties and could provide passive or active targeting or sustained delivery. Biomedical applications of the developed carriers are continuously growing (Ahmad, 2013; Soares, 2013; Miladi et al., 2013). Although, they present different physicochemical properties, the used polymers are mainly biocompatible and biodegradable. A multitude of techniques are used to obtain these particles. These methods differ by their principles and the nature of drug molecules that could be encapsulated. Some successfully marketed products led to an enlargement of the applications and the interest given by researchers to these drug delivery systems. Choice of the technique and operating conditions is crucial to obtain formulations bearing good properties for *in vitro* and *in vivo* applications. In this review, we will focus on polymeric particles and give a scope about the most used polymers. We will also describe the common preformed polymer based techniques used

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for the encapsulation of drug molecules. We will also review the major applications of the developed particles during the last years and their main properties.

1. POLYMER-SOLVENT INTERACTIONS

Many techniques that rely on preformed polymers have been used for the preparation of particulate carriers. Although these methods are quite different, they generally share a unique principle which is polymer precipitation. Precipitation of the polymer occurs either when a non solvent is added or after subsequent decrease of its solubility in a solvent. Many parameters could influence polymer solubility such as, solvent nature, pH, salinity and temperature of the dispersion medium. Solubility of polyelectrolytes in water, for example, is highly pH and salinity dependent (Gennes, 1979), while that of poly(alkyl acrylamide) and poly(alkyl methacrylamide), is mainly temperature dependent (Elaissari, 2002). In fact, nanoprecipitation and emulsion based techniques are based on the addition of a non solvent to the polymer which causes its precipitation. However, ionic gelation technique, for instance, in which generally a polyelectrolyte is used as polymer, is based on the addition of a salt or an oppositely charged polymer. This results in a change in the salinity of the medium and the appearance of electrostatic interactions and thus, leads to polymer precipitation. The thermodynamic behavior of the polymer in a given solution is highly dependent on the Flory χ-parameter. This parameter is defined as the free energy change per solvent molecule (in k_BT units) when a solvent-solvent contact is shifted to a solvent-polymer contact. It is expressed by the following mathematical equations:

$$\chi = \frac{\Delta G}{k_B T} = \frac{\Delta H - T\Delta S}{k_B T} = \frac{1}{2} - A\left(1 - \frac{\theta}{T}\right)$$

Equation (1)

where kB and T are Boltzmann constant and temperature, respectively; A and θ parameters are defined as follows:

$$A = \frac{2\Delta S + k_B}{2k_B}$$ Equation (2)

$$\theta = \frac{2\Delta H}{2\Delta S + k_B}$$ Equation (3)

It can be seen that the A parameter is directly related to entropy changes, whereas θ temperature is a function of both entropic and enthalpic variations. When θ temperature = T, the corresponding Flory χ-parameter = 1/2, at which the second Virial coefficient is equal zero (Elias, 2003). The latter can be easily determined from light scattering measurements of a diluted polymer solution. At θ temperature conditions, the binary interactions among constituents will be negligible and only the excluded volume effects will be predominant. Consequently, the solvent will be a good solvent for the polymer when $\chi < 1/2$ and a poor one when $\chi > 1/2$ (Minost et al., 2012).

2. COMMONLY USED POLYMERS FOR ENCAPSULATION

Several polymers have been used for drug encapsulation but only biodegradable and biocompatible ones are suitable for biomedical applications. The biodegradability of a polymer is acquired by the presence of a labile function such as ester, orthoester, anhydride, carbonate, amide, urea or urethane in their backbone. These polymers could be of natural (polysaccharides and protein based polymers) or synthetic (polyesters) nature (Pillai and Panchagnula, 2001). The most commonly used polymers for drug encapsulation are polyesters (lactide and glycolide copolymers, poly-ε-caprolactone), acrylic polymers (polymethacrylates) and polyamides (gelatin and albumin). The selection of the right polymer is a crucial step to obtain particles that are suitable for a well-defined application. In fact, polymers' structures are highly differ-

ent and their surface and bulk properties are highly relevant for the obtaining of the desirable biological application. Copolymers could be also used to monitor the hydrophobicity of the materials. Some polymers are poly(ethyleneglycol) (PEG) copolymerized in order to decrease nanoparticle recognition by the reticular endothelial system. Table 1 contains examples of the most used biocompatible and biodegradable polymers in encapsulation. Some polymers, especially those having mucoadhesive properties, could also be used for coating the nanocarriers (Mazzaferro et al., 2012; Zandanel and Vauthier, 2012).

Table 1: Commonly used polymers

Materials	References
Polymers	
Natural polymers	
Chitosan	Elmizadeh et al., 2013; Fàbregas et al., 2013; Khalil et al., 2012; Konecsni et al., 2012; Du et al., 2009; Bernkop-Schnürch et al., 2006; Gan et al., 2005; Asada et al., 2004
Dextran	Liang et al., 2013; Dai et al., 2012; Sajadi Tabassi et al., 2008; Koten et al., 2003
Dextran derivatives	Kanthamneni et al., 2012; Kauffman et al., 2012; Aumelas et al., 2007; Miyazaki et al., 2006
Cyclodextrins	Çirpanli et al., 2009; Memişoğlu et al., 2003; Pariot et al., 2002; Lemos-Senna et al., 1998
Gelatin	Nahar et al., 2008; Balthasar et al., 2005; Vandervoort and Ludwig, 2004; Bruschi et al., 2003
Synthetic polymers	
Biodegradable polyesters	
PLGA	Gyulai et al., 2013; Beck-Broichsitter et al., 2012; Morales-Cruz et al., 2012; Beck-Broichsitter et al., 2011; Nehilla et al., 2008; Song et al., 2008; Budhian et al., 2007; Bozkir and Saka, 2005; Fonseca et al., 2002;Yang et al., 1999; Govender et al., 1999
PLA	Bazylińska et al., 2013; Fredriksen and Grip 2012; Kadam et al., 2012; Kumari et al., 2011; Ataman-Önal et al., 2006; Lamalle-Bernard et al., 2006; Hyvönen et al., 2005; Katare et al., 2005; Chorny et al., 2002; Leo et al., 2000
PCL	Behera and Swain, 2012; Guerreiro et al., 2012; Hernán Pérez de la Ossa et al., 2012; Khayata et al., 2012; Arias et al., 2010; Wang et al., 2008; Limayem Blouza et al., 2006; Tewa-Tagne et al., 2006; Yang et al., 2006; Le Ray et al., 2003; Chawla and Amiji 2002; Raval et al., 2011; Hombreiro Pérez et al., 2000; Benoit et al., 1999; Masson et al., 1997
Poly(lactide-co-glycolide-co-caprolactone)	Zhang et al., 2006
Acrylic polymers	
Eudragit	Hao et al., 2013; Das et al., 2010; Eidi et al., 2010; Trapani et al., 2007; Galindo-Rodríguez et al., 2005; Haznedar and Dortunç 2004; Pignatello et al., 2002
Others	
Polyvinylbenzoate	Labruère et al., 2010
Pegylated polymers	
Chitosan-PEG	Seo et al., 2009
MPEG-PCL	Falamarzian and Lavasanifar, 2010; Xin et al., 2010
PCL-PEG-PCL	Suksiriworapong et al., 2012; Huang et al., 2010; Gou et al., 2009
Poly(caprolactone)-poly(ethylene oxide)-polylactide	Hu et al., 2003
PLA-PEG	Sacchetin et al., 2013; Essa et al., 2010; Ishihara et al., 2010; Vila et al., 2005; Vila et al., 2004; Govender et al., 2000; Huang et al., 1997
PLA-PEG-PLA	Chen et al., 2011; Ruan and Feng 2003
MPEG-PLA	Zheng et al., 2010; Dong and Feng, 2007; Dong and Feng, 2004

2.1 Natural polymers

2.1.1 Chitosan

Chitosan is obtained by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (crabs, shrimp, etc.) and cell walls of fungi. It is a cationic and biodegradable polysaccharide consisting of repeating D-glucosamine and N-acetyl-D-glucosamine units, linked via (1-4) glycosidic bonds. Chitosan is non toxic and can be digested in the physiological environment, either by lysozymes or by chitinases, which are present in the human intestine and in the blood. These properties led to increased interest for this polymer in pharmaceutical research and industry as a carrier for drug delivery (Mao et al., 2010). In addition, chitosan has mucoadhesive properties owing to its positive charge that allows interaction with the negatively-charged mucosal surface. Consequently, the use of chitosan as a matrix (Patil and Sawant, 2011) or as a coating material (Mazzarino et al., 2012) in drug encapsulation had become a promising strategy to prolong the residence time, to increase the absorption of active molecules through the mucosa (Mao et al., 2010; Alpar et al., 2005) and also for targeted delivery (Park et al., 2010).

2.1.2 Dextran and its derivatives

Dextran polymers are produced by bacteria from sucrose. Chemical synthesis is also possible. These glucose polymers consist predominantly of linear α-1,6-glucosidic linkage with some degree of branching via 1,3-linkage. Dextran-based microspheres have got much attention because of their low toxicity, good biocompatibility and biodegradability, which are of interest for application in biomedical and pharmaceutical fields (Mehvar, 2000). Many detxran polymers such as Sephadex® (cross-linked dextran microspheres) as well as Spherex® (cross-linked starch microspheres) were used as carriers for drug delivery. Other derivatives of dextran and starch including diethyl aminoethyl dextran and polyacryl starch have also been used for mucosal drug delivery. Illum et al. (2001) proposed some mechanisms to explain absorption enhancement effects of cross-linked starch and dextran microspheres intended to nasal delivery which are: (1) Deposition of the microspheres in the less or non ciliated anterior part of the nasal cavity and slower nasal clearance; (2) Retention of the formulation in the nasal cavity for an extended time period because of the bioadhesive properties of the microspheres and (3) The local high drug concentration provided by the gelled system in close contact with the epithelial absorptive surface (Illum et al., 2001).

2.1.3 Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides that contain at least six D-(+) glucopyranose units which are attached by α-(1,4) glucosidic bonds. They have been widely used for the formulation of drugs with bioavailability concerns resulting from poor solubility, poor stability and severe side effects. There are 3 natural CDs which are α-, β-, and γ-CDs (with 6, 7, or 8 glucose units respectively) (Challa et al., 2005). In addition, amphiphilic cyclodextrins are synthetic derivatives of natural cyclodextrins. Such derivatives are able to self-organize in water to form micelles and nano-aggregates, which is interesting for pharmaceutical applications, mainly, encapsulation (Gèze et al., 2002). In fact, amphiphilic cyclodextrins have recently been used to prepare nanoparticles and nanocapsules without surfactants and have shown high drug-loading capacity with favorable release properties (Lemos-Senna et al., 1998; Çirpanli et al., 2009; Duchêne, 1999). They have also been used for targeting and for increasing drug loading (Duchêne et al., 1999).

2.1.4 Gelatin

Gelatin is a natural polymer that is derived from collagen. It is commonly used for pharmaceutical and medical applications because of its biodegradability and biocompatibility in physiological environments. Gelatin is attractive for use in controlled release due to its nontoxic, bioactive properties and inexpensive price. It is also a polyampholyte having both cationic and anionic groups along with hydrophilic groups. Mechanical properties, swelling behavior and thermal properties of gelatin depend significantly on its crosslinking degree (Young et al., 2005).

2.2 Biodegradable polyesters

Polyester-based polymers are among of the most widely investigated materials for drug delivery. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers poly(lactic acid-co-glycolic acid) (PLGA) along with poly-ε-caprolactone are some of the well-defined biomaterials with regard to design and performance for drug-delivery applications.

2.2.1 PLGA

PLGA, a copolymer of lactic acid and glycolic acid, has generated tremendous interest due to its excellent biocompatibility, biodegradability, and mechanical strength. PLGA is approved by the US FDA and European Medicine Agency (EMA) in various drug delivery systems in humans. In order to improve the formulation of controlled drug delivery systems, an understanding of the physical, chemical, and biological properties of polymers is helpful. In fact, the polymer is commercially available with different molecular weights and copolymer compositions. The degradation time can vary from several months to several years, depending on the molecular weight and copolymer ratio (Danhier et al., 2012). For example, lactic acid is more hydrophobic than glycolic acid and, therefore, lactide-rich PLGA copolymers are less hydrophilic, absorb less water, and subsequently, degrade more slowly (Dinarvand et al., 2011). PLGA particles are widely used to encapsulate active molecules with a broad spectrum of pharmaceutical applications (Danhier et al., 2012; Menei et al., 2005; Singh et al., 2004).

2.2.2 PLA

PLA is a biocompatible and biodegradable synthetic polyester which undergoes scission in the body to monomeric units of lactic acid. The latter is a natural intermediate in carbohydrate metabolism. PLA possess good mechanical properties and it is largely used for the preparation of particles (Gupta and Kumar, 2007).

2.2.3 PCL

It was in 1930s that the ring-opening polymerization of PCL was studied. The biodegradable property of this synthetic polymer was first identified in 1973. PCL is suitable for controlled drug delivery due to its high permeability to many drugs and non-toxicity (Sinha et al., 2004). Molecular weight dependent surface hydrophobicity and crystallinity of PCL are the causes for its slower biodegradation in two distinct phases such as random non-enzymatic cleavage and enzymatic fragmentation. Lipophilic drugs are generally distributed uniformly in the matrix while hydrophilic drugs tend to move towards the interface and remain on the surface of PCL formulation in adsorbed state. Diffusion was described as the only possible mechanism by which the lipophilic drugs release from PCL particles as they were shown to be intact for a much longer duration *in vivo*. However, two phenomena could be implicated in hydrophilic drugs' release. Highly lipophilic drugs that resist complete diffusion are released upon surface erosion by enzymatic action while hydrophilic drugs that accumulate at the interface during the formulation processes are released by desorption at the initial period of release study

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or dosage intake. This results in a biphasic drug release pattern for PCL particles with much higher burst release for hydrophilic drugs than lipophilic ones (Dash and Konkimalla, 2012).

2.3 Pegylated polymers

Many of the above cited polymers could be conjugated to PEG chains, which allows the enhancement of their hydrophilicity and permits the obtaining of a stealth surface that could protect the prepared carriers from degradation by the cells belonging to the reticuloendothelial system. Conjugation to PEG confers also bioadhesive properties for the carriers (Yoncheva et al. 2005).

3. Used methods for the encapsulation of active molecules

3.1 Nanoprecipitation

The nanoprecipitation technique was first developed by Fessi et al. in 1986 (Devissaguet et al., 1991). The technique allows the obtaining of either nanospheres or nanocapsules. The organic phase could be added to the aqueous phase under magnetic stirring. This one-step process allows the instantaneous and reproducible formation of monodisperse nanoparticles. Nanoprecipitation is simple, is by far the fastest, most reproducible, and industrially feasible preparation procedure of nanospheres (Vauthier and Bouchemal, 2009). Practically, two miscible phases are required: an organic solvent in which the polymer is dissolved and an aqueous phase (non-solvent of the polymer). The most common used organic solvents are ethanol and acetone. Such solvents are miscible in water and easy to remove by evaporation. Some oils could be added to these solvents to allow the dissolving of the active (Rosset et al., 2012). As Figure 1 shows, the method is based on the addition of one phase to the other under moderate magnetic stirring which causes the interfacial deposition of a polymer after displacement of the organic solvent from the organic solution. This leads to the formation of a suspension of nanoparticles. The organic phase could be a mixture of solvents such as, mixture of acetone with water or ethanol etc. Similarly, the aqueous phase could consist of a mixture of non-solvents and could contain surfactants. Commonly used polymers are biodegradable polyesters, especially PCL, PLA and PLGA (Rao and Geckeler, 2011). Particle formation process includes three basic steps which are, particle nucleation, molecular growth and aggregation. The rate of every step has a crucial impact on the particle size distribution. Supersaturation is the driving force that manages all of these steps, namely, particles nucleation rate. Supersaturation, itself, is influenced by fluid dynamics and mixing. In fact, low stirring rate results in low nucleation rates while higher mixing rates give high nucleation rates (Lince et al., 2008).

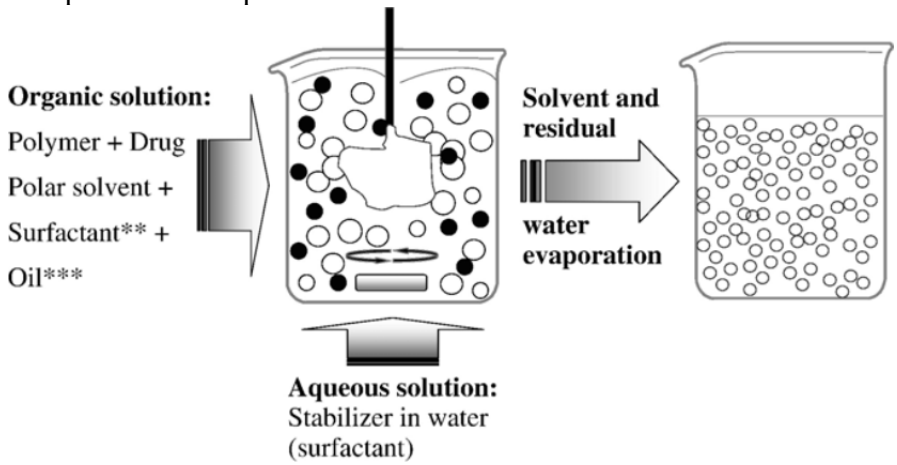

Figure 1: The nanoprecipitation technique (Pinto Reis et al., 2006)

Operational parameters that should be controlled include the organic phase to non organic phase ratio, the concentration of the polymer and the stabilizer and the amount of the drug. Every one of these parameters may exert an impact on the characteristics of the obtained nanoparticles (size, uniformity and charge). In fact, an increase of the polymer amount generally increases particles' size (Chorny et al., 2002; Simşek et al., 2013; Dong and Feng, 2004; Asadi et al., 2011). The same effect was obtained after increasing the polymer molecular weight (Limayem Blouza et al., 2006; Holgado et al., 2012). These findings were explained by an increase of the viscosity of the organic phase which rendered solvent diffusion more difficult and thus, led to larger nanoparticles' size. The effect of increasing organic phase volume seems conflicting: some studies showed that it causes a decrease of the particles size (Dong and Feng, 2004) while others showed the opposite phenomenon (Asadi et al., 2011). Increasing the water phase amount leads to a decrease of the particles size as a result of the increased diffusion of the water-miscible solvent in the aqueous phase and thus, the more rapid precipitation of the polymer and formation of nanoparticles (Budhian et al., 2007). An increase of the surfactant amount generally causes a decrease of the particles size and reduces size distribution (Contado et al., 2013; Siqueira-Moura et al., 2013). Some studies did not, however, found significant change following surfactant amount increase (Dong and Feng, 2004). The nature of the surfactant may also influence the particles' size (Limayem Blouza et al., 2006). Increasing mixing rate decreases the particles size as it causes faster diffusion rate (Asadi et al., 2011). Theoretical drug loading may also influence particles size and drug loading (Govender et al., 1999). Nanoprecipitation is generally designed for the encapsulation of hydrophobic drug molecules (Seju et al., 2011; Katara and Majumdar, 2013; Seremeta et al., 2013). Such actives may be dissolved within the organic phase. Bilalti et al. (2005) described a nanoprecipitation technique intended to the encapsulation of hydrophilic molecules but the size of the obtained particles was not sufficiently uniform (Bilati et al., 2005). To further improve the reproducibility of the nanoprecipitation technique and make it more convenient for industrial applications, membrane contactor and microfluidic technology were successfully used (Khayata et al., 2012; Xie and Smith, 2010). These techniques allow better size control within different batches of particles. Table 2 contains some examples of the applications of the nanoprecipitation technique in drug delivery during the last years. It can be concluded that polyesters are among the most used polymers for the preparation of the nanoparticles by this technique.

3.2 Emulsion diffusion (ESD)

ESD was first developed by Quintanar-Guerrero and Fessi (Quintanar-Guerrero et al., 1996) to prepare PLA based nanospheres. Three liquid phases are needed in this technique: an organic phase, an aqueous phase and a dilution phase. The organic phase generally contains the polymer and the hydrophobic drug. The aqueous phase is a solution of a stabilizing agent while the dilution phase usually consists of a large volume of water. Mutual saturation of the aqueous and organic phase allows further obtaining of a thermodynamically equilibrated emulsion upon high speed homogenization. Subsequent addition of an excess of water enables the diffusion of the organic solvent from the dispersed phase resulting in precipitation of the polymer and the formation of the particles (Figure 2). Commonly used polymers in this method include PCL, PLA and Eudragit® (Mora-Huertas et al., 2010). Table 3 shows that the technique is mainly used for the encapsulation of hydrophobic molecules. However, hydrophilic molecules may also be encapsulated by a modified solvent diffusion method using an aqueous inner phase (Ma

et al., 2001). Operating conditions affecting the size of the obtained particles include external/internal phase ratio, emulsification stirring rate, volume and temperature of water for dilution, polymer amount and concentration of the stabilizer (Quintanar-Guerrero et al., 1996; Mora-Huertas et al., 2010). Influence of high shear homogenization and sonication on the particles size was assessed and it was found that sonication was more efficient for particle size reduction. The nature of the surfactant influenced also the particles size. In fact, when Pluronic F68 (PF68), didodecyldimethylammonium bromide (DMAB) and polyvinylalcohol (PVA) were compared, DMAB gave the smallest particles but with the lowest encapsulation efficiency (Jain et al., 2011). Particles size was also described to increase with an increase of initial drug amount (Youm et al., 2012), polymer amount (Youm et al., 2012; Esmaeili et al., 2011) and the oil phase volume (Esmaeili et al., 2011; Poletto et al., 2008). An increase of the surfactant amount resulted in a decrease of the size but it seems that above some level further significant size reduction is no longer possible (Jain et al., 2011; Surassmo et al., 2010). An increase of the homogenization rate led to a decrease of the particles' size (Jain et al., 2011; Kwon et al., 2001; Galindo-Rodríguez et al., 2005). Likely, the same effect was obtained following an increase of the temperature and the volume of added water (Kwon et al., 2001; Song et al., 2006). The nature of the organic solvent also influenced particle size (Song et al., 2006). Table 3 shows some of the recent applications of the ESD technique.

Table 2: Applications of the nanoprecipitation technique

Encapsulated molecule	Polymer	Size (nm)	Zeta potential (mV)	Reference
Doxorubicin	Gelatin-co-PLA-DPPE	131.5-161.1	-	Han et al., 2013
Aceclofenac	Eudragit RL 100	75.5-184.4	22.5 - 32.6	Katara and Majumdar, 2013
Doxorubicin	Dextran-b-polycaprolactone	95-123.3	-	Li et al., 2013
Chloroaluminum phthalocyanine	PLGA	220.3-326.3	-17.7-(-40.9)	Siqueira-Moura et al., 2013
Efavirenz	PCL and Eudragit® RS 100	89.5 - 173.9	-17.9-53.8	Seremeta et al., 2013
Paclitaxel	PLGA	50 - 150	-15 - (-20)	Wang et al., 2013
Retinoic acid	PLA	153.6-229.8	-27.4-(-20.9)	Almouazen et al., 2012
Brimonidine Tartrate	Eudragit® RL 100	123.5 - 140.2	13.1- 20.8	Khan et al., 2012
Vitamin E	PCL	123-320	-24.5-(-1.46)	Khayata et al., 2012
Paclitaxel	Hydrophobized pullulan	127.6-253		Lee et al., 2012
Curcumin	PCL, chitosan	104-125	(-0.099)-79.8	Mazzarino et al., 2012
Diclofenac	PCL	152	-50	Mora-Huertas et al., 2012
Amphotericin B	PLGA	86-153	-31.4-(-9.1)	Van de Ven et al., 2012
Epirubicin	Poly(butyl cyanoacrylate)	217-235	-4.5-(-0.1)	Yordanov 2012
Camptothecin	Beta-cyclodextrin PLGA PCL	281 187 274	-13 -0.06 -19	Cırpanlı et al., 2011
Naringenin	Eudragit® E	90	-	Krishnakumar et al., 2011
Olanzapine	PLGA	91.2	-23.7	Seju et al., 2011

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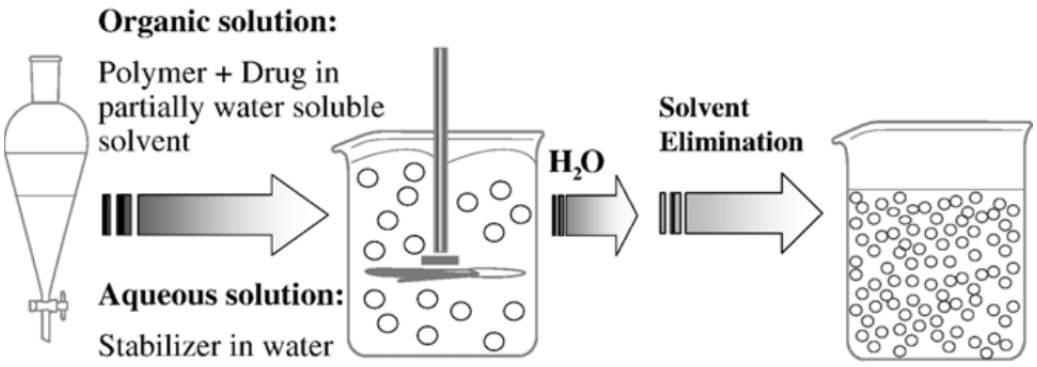

Figure 2: Emulsion diffusion technique (Pinto Reis et al., 2006)

Table 3: Applications of the emulsion diffusion method

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Articaine	PCL	-	-	Campos et al., 2013
Omeprazole	Eudragit L 100-55	0.256.3- 0.337	8.92 - 16.53	Hao et al., 2013
Curcumin	Polyurethane and polyurea	0.216- 4.901	-	Souguir et al., 2013
Matricaria recutita L. extract	PEG-PBA-PEG	0.186- 0.446	-	Esmaeili et al., 2011
Bovine serum albumin	Chitosan	81-98	-	Karnchanajindanun et al., 2011
Alendronate	PLGA	0.145	-4.7	Cohen-Sela et al., 2009
An oligonucleo-tide	PLA	0.390	-	Delie et al., 2001

3.3 Simple Emulsion evaporation (SEE)

The SEE technique is widely used in the field of particulate carriers' development. This method was first developed by (Vanderhoff et al., 1979). It consists on the formation of a simple emulsion followed by the evaporation of the organic solvent. Subsequent precipitation of the polymer allows the obtaining of the particles (Figure 3). Practically, for oil in water emulsion method, the polymer is dissolved in a volatile and non miscible organic solvent such as chloroform, ethylacetate or dichloromethane. This organic phase, in which the drug and the polymer are dissolved, is then dispersed by high speed homogenization or by sonication in an aqueous phase containing a surfactant. Once an oil-in-water (o/w) emulsion is obtained, the evaporation of the organic solvent permits the precipitation of the polymer and thus, the formation of the particles. As it can be seen in Table 4, SEE is generally used for the encapsulation of hydrophobic drugs (O'Donnell and McGinity, 1997). The evaporation of the organic solvent is obtained by moderately stirring the emulsion at room temperature or under high temperature and low pressure conditions. The obtained particles can be then harvested by ultracentrifugation or filtration, then washed and lyophilized. Membrane technology was also used to prepare particles by the simple emulsion technique (Doan et al., 2011). Another alternative of the technique is the use of water in oil emulsion method that is suitable for the encapsulation of hydrophilic active molecules. Particulate carriers are obtained after evap-

oration of the water phase which causes the precipitation of the hydrophilic polymer (Banerjee et al., 2012). Parameters that have to be managed include organic phase to water phase ratio, nature of the surfactant and its concentration, stirring rate, polymer amount and evaporation rate. Decreasing the organic solvent volume resulted generally in a decrease of particle size (Budhian et al., 2007). Particle size could also be decreased by increasing surfactant amount (Valot et al., 2009; Manchanda et al., 2010; Khaled et al., 2010; Su et al., 2009), increasing stirring rate (Su et al., 2009; Lee et al., 2012; Avachat et al., 2011; Yadav and Sawant, 2010) or increasing aqueous phase volume (Adibkia et al., 2011). However, an increase of polymer amount generally increases particles' size (Doan et al., 2011; D'Aurizio et al., 2011; Adibkia et al., 2011; Agnihotri and Vavia, 2009). Table 4 shows the applications of the SEE technique in drug delivery. Polyesters were widely used for the encapsulation of hydrophobic drugs.

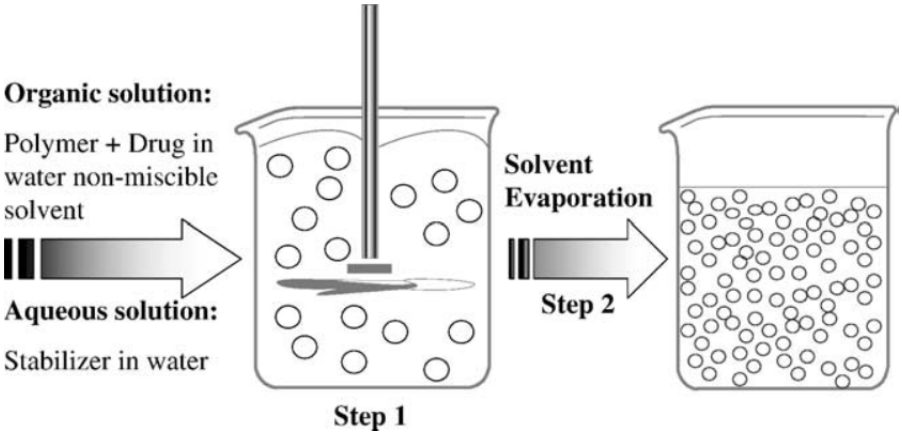

Figure 3: Simple emulsion solvent evaporation (Pinto Reis et al., 2006)

Table 4: Applications of simple emulsion solvent evaporation technique

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Curcumin	PLGA and PLGA-PEG	0.161-0.152	-	Khalil et al., 2013
Efavirenz	PCL and Eudragit® RS 100	0.083-0.219	53	Seremeta et al., 2013
Human amylin	PCL	0.202	-	Guerreiro et al., 2012
Azithromycin	PLGA	14.11-15.29	-	Li et al., 2012
Teniposide	PLGA	0.113-0.135	-36.6-(-23.1)	Mo et al., 2012
Camptothecin	PCL-PEG-PCL	4.2-5.4	-	Dai et al., 2011
Naproxen	PLGA	352-824	-	Javadzadeh et al., 2010
Doxorubicin	PLGA	0.137-0.164	-12.3-(-9.9)	Manchanda et al., 2010
Dexamethasone	PLGA	5.18-7	-	Rawat and Burgess, 2010
Ibuprofen	Eudragit RSPO	14-51.1	-	Valot et al., 2009

3.4 Double emulsion evaporation (DEE)

Double emulsion technique is suitable for the encapsulation of hydrophilic molecules (see Table 5 and Figure 4). Generally, the method consists on the dispersion of an aqueous phase in a non miscible organic solvent to form the first emulsion (W1/O). This dispersion is performed under high shear homogenization or low power sonication for a short time. This step is followed by the dispersion of the obtained emulsion in a second aqueous phase containing a hydrophilic emulsifier. Again, homogenization could be carried under high shear homogenization or with a sonication probe. When sonication is used, it must be performed at low power and within a short period of time to not break the first emulsion (Giri et al., 2013). After the formation of the multiple emulsion, evaporation of the volatile organic solvent under low pressure (by a rotary evaporator) or at ambient temperature allows the obtaining of the particulate carriers (Figure 4). There are other types of multiple emulsions like w/o/o or o/w/o (Giri et al., 2013). A lot of parameters may influence the properties of the obtained particles such as, relative phases' ratio (Khoee et al., 2012), amount of the polymer, its nature and molecular weight (Zambaux et al., 1998; Péan et al., 1998; Van de Ven et al., 2011), nature of the surfactants and their amounts (Zhao et al., 2007; Khoee and Yaghoobian, 2009; Dhanaraju et al., 2004), homogenization speed (Eley and Mathew, 2007; Basarkar et al., 2007), the composition of the external phase (Péan et al., 1998; Tse et al., 2009) and evaporation speed (Khoee et al., 2012). Operating conditions may also influence strongly encapsulation efficiency (Tse et al., 2009; Billon et al., 2005; Silva et al., 2013; Zhou et al., 2013; Karataş et al., 2009; Hachicha et al., 2006; Al-Kassas, 2004; Cun et al., 2011; Gaignaux et al., 2012; Cun et al., 2010). Membrane technique and microfluidic devices were also used to prepare particulate carriers by the DES method (Vladisavljević and Williams, 2008; van der Graaf et al., 2005).

3.5 Spray drying

Spray drying is a simple process which gained too much interest due to its cost-effectiveness and scalability (Sou et al., 2011). Practically, a polymer containing drug solution is atomized and sprayed into a drying chamber where droplets are dried by heated air (See Figure 5). Reduction of droplets' size that follows atomization allows the obtaining of an enormous surface area between droplets and the drying gas. The subsequent precipitation of the polymer permits the encapsulation of the drug within the obtained particulate carriers. The evaporation of the solvent occurs within a very short period of time. Consequently, the materials never reach the inlet temperature of drying gas. This is very attractive for encapsulating heat-sensitive drug molecules like proteins (Cal and Sollohub, 2010; Sollohub and Cal, 2010; Prata et al., 2013). Many operating conditions could influence the properties of the obtained particles. Parameters to be controlled include the drying air temperature and humidity (Bruschi et al., 2003), the rate and fluid dynamics of the air flow, the atomization process (Droplet size, spray rate, spray mechanism) and the composition of ingredients and excipients in the feeding solution (Rattes and Oliveira, 2007). PLA (Baras et al., 2000; Gander et al., 1996; Sastre et al., 2007; Muttil et al., 2007), PLGA (Wang and Wang, 2002; Mu and Feng, 2001; Castelli et al., 1998; Bittner et al., 1999; Prior et al., 2000; Conti et al., 1997), PCL, methacrylate polymers (Esposito et al., 2002; Año et al., 2011; Cruz et al., 2010; Hegazy et al., 2002; Raffin et al., 2008) and chitosan (He et al., 1999; Giunchedi et al., 2002; Cevher et al., 2006) are among the most used polymers in spray-drying method. As Table 6 shows, the technique allowed the obtaining of mainly microparticles bearing better drug solubility and sustained release.

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Table 5: Applications of the double emulsion technique

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Vancomycin	PLGA	0.450-0.466	-7.2-(-3.5)	Zakeri-Milani et al., 2013
Prostaglandin E1	PLGA	7-22.5	-	Gupta and Ahsan, 2011
Deoxyribonuclease I	PLGA	0.190-0.349	-	Osman et al., 2011
S. equi antigens	PCL	0.242-0.450	-53.1-38.7	Florindo et al., 2009
Hepatitis B surface antigen	PLGA	1-5	0.51-14	Thomas et al., 2009
Plasmid DNA	PLGA	1.9-4.6	-24.6-(-22.9)	Tse et al., 2009

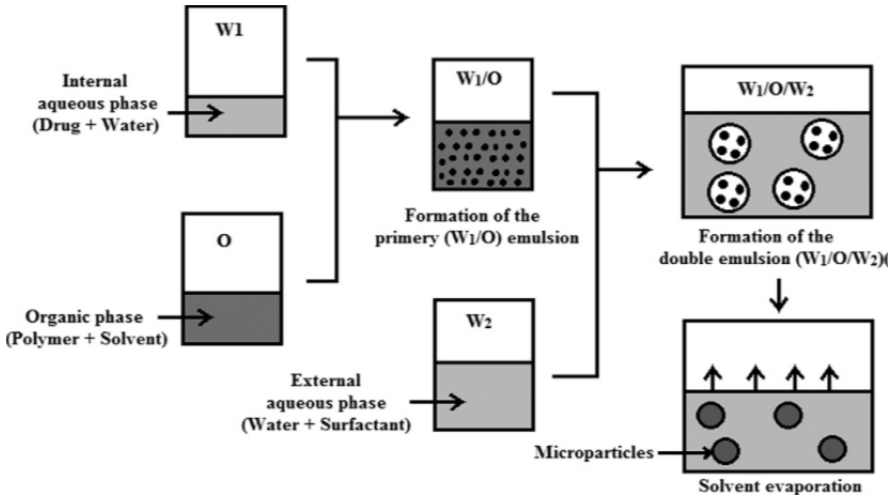

Figure 4: Double emulsion solvent evaporation technique (Giri et al., 2013)

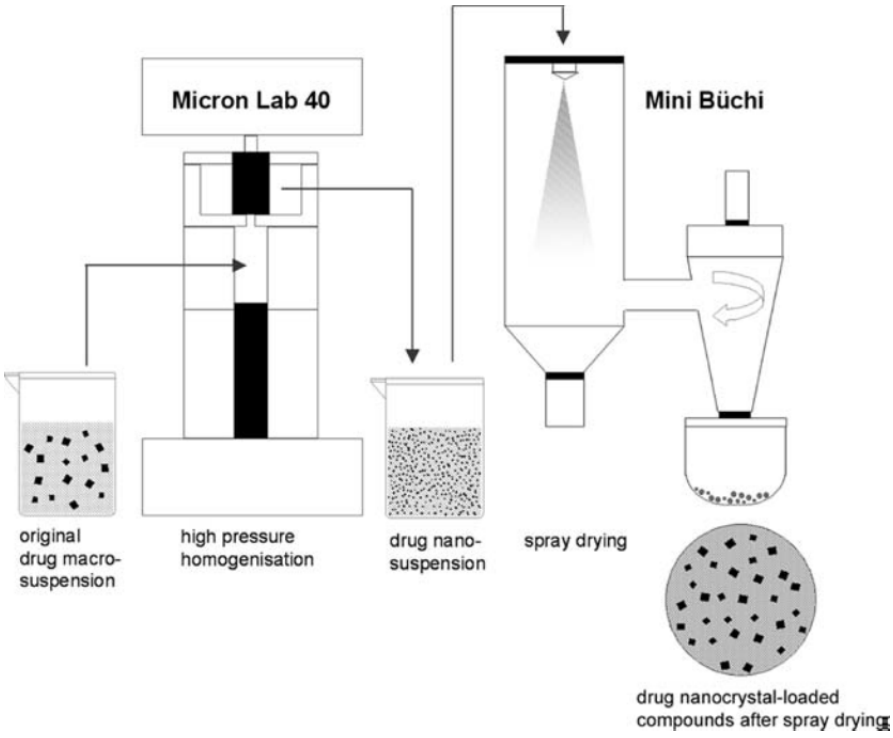

Figure 5: The spray drying method (Pinto Reis et al., 2006)

Table 6: Applications of the spray drying technique

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Nimodipine	PLGA	1.9-2.37	-	Bege et al., 2013
Theophylline	Eudragit RS30D	< 60	-	Garekani et al., 2013
Ofloxacin	PLA	2.6-4.9	-	Palazzo et al., 2013
Sodium diclofenac	PGA-co-PDL PEG-PGA-co-PDL and mPEG-co-(PGA-co-PDL)	2.3 3.9 2.5	-32.2 -29.9 -31.2	Tawfeek, 2013
Sodium fluoride	Chitosan	3.4-5.3	-	Keegan et al., 2012
Plasmid	Chitosan	2.5-11.7	-	Mohajel et al., 2012
Heparin	PLGA	2.5-3.8	-63.5 - (-28.2)	Yildiz et al., 2012
Alendronate	Eudragit® S100	13.8	-	Cruz et al., 2010
Zolmitriptan	Chitosan glutamate and Chitosan base	2.6-9.4	-	Alhalaweh et al., 2009
Triamcinolone	PLGA	0.5-1.5	-	da Silva et al., 2009
Acyclovir	Chitosan	18.7-34.9	-	Stulzer et al., 2009

3.6 Supercritical fluid technology (SFT)

In the recent years, novel particle formation techniques using supercritical fluids (SCF) have been developed in order to overcome some of the disadvantages of conventional techniques that are: (1) poor control of particle size and morphology; (2) degradation and lost of biological activity of thermo sensitive compounds; (3) low encapsulation efficiency and (4) low precipitation yield (Santos et al., 2013). Moreover, SFT presents the main advantage of not requiring the use of toxic solvents. In fact, SCF based technologies have attracted enormous interest for the production of microparticles and nanoparticles (Table 7), since their emergence in the early 1990s (Sanli et al., 2012).

The supercritical state is achieved when a substance is exposed to conditions above its critical pressure and temperature. In such conditions, the fluid will have liquid-like density and, thus, solvating properties that are similar to those of liquids and, at the same time, gas-like mass transfer properties. Carbon dioxide (CO_2) is the most commonly used critical fluid. In fact, CO_2 is nontoxic, nonflammable and easy recyclable. Moreover, CO_2 has moderate critical parameters of CO_2 (a critical pressure of 7.4 MPa and a critical temperature of 304.1 K) and low price and is highly available which makes it very attractive from an economical point of view and also for the processing of labile compounds (Elizondo et al., 2012). Supercritical fluid technology methods can be divided in four methods which are rapid expansion of supercritical solution (RESS), Particles from gas saturated solutions (PGSS), gas antisolvent (GAS) and supercritical antisolvent process (SAS). These methods depend on whether CO_2 was used as a solvent, a solute or an antisolvent. Figure 6 shows the experimental set up of the RESS technique. In the RESS technique, the drug and the polymer are first dissolved in supercritical CO_2 in high pressure chamber. The subsequent passing of the solution through a nozzle results in a rapid decrease of the pressure and thus, a precipitation of the drug particles embedded in the polymer matrix and their recovery in the extraction unit (Byrappa et al., 2008). Many parameters such as the density of the SCF (Pressure and temperature of supercritical fluid) (Kalani and Yunus, 2012), flow rate of drug-polymer solution and/or CO_2 and formulation variables (Martin et al., 2002) could influence the size of the obtained particles. Table 7 shows that SFT was used for

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the processing of nanoparticles and microparticles mainly based on polyesters.

3.7 Ionic gelation (IG)

IG method is used mainly with natural hydrophilic polymers to prepare particulate carriers. These polymers include gelatin, alginate, chitosan and agarose. IG has the advantage of not using organic solvents. The technique is based on the transition of the polymer from liquid state to a gel (Figure 7). For instance, gelatin based particles are obtained after the hardening of the droplets of emulsified gelatin solution. The particles are obtained after cooling gelatin emulsion droplets below the gelation point in an ice bath. For alginate, however, particles are produced by drop-by-drop extrusion of the sodium alginate solution into the calcium chloride solution. Sodium alginate is, in fact, a water-soluble polymer that gels in the presence of multivalent cations such as calcium. Chitosan particles are prepared by spontaneous formation of complexes between the positively charged chitosan and polyanions (tripolyphosphate or gelatin) or by the gelation of a chitosan solution dispersed in an oil emulsion (Mahapatro and Singh, 2011). Figure 7 illustrates the gelation mechanism of polysaccharides. At high temperatures, a random coil conformation is assumed. With decreasing temperature, the aggregation of double helices structure forms the physical junctions of gels (Rees and Welsh, 1977). Table 8 displays some recent applications of IG. This technique has been mainly used to prepare chitosan nanoparticles.

Table 7: Applications of the SCF technology

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Hydrocortisone acetate	PLGA	1-5	-	Falco et al., 2013
17α-methyltestosterone	PLA	5.4-20.5	13.9 - 67.7	Sacchetin et al., 2013
Paracetamol	PLA	0.301-1.461	-	Kalani and Yunus, 2012
5-fluorouracil	PLLA-PEG/PEG	0.175	-	Zhang et al., 2012
Human growth hormone	PLGA	93	-	Jordan et al., 2010
Azacytidine	PLA	2	-	Argemí et al., 2009
Bovine serum albumin	PLA	2.5	-	Kang et al., 2009
Retinyl palmitate	PLA	0.040-0.110	-	Sane and Limtrakul, 2009
Indomethacin	PLA	2.35	-	Kang et al., 2008

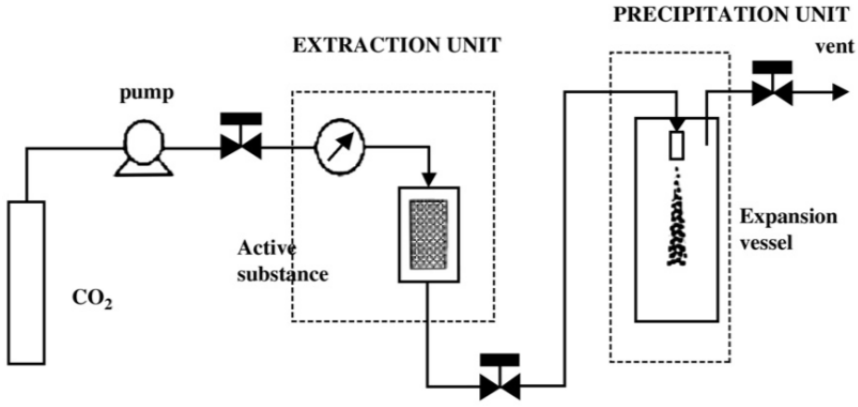

Figure 6: Schematic presentation of the experimental set up for the RESS process (Byrappa et al., 2008)

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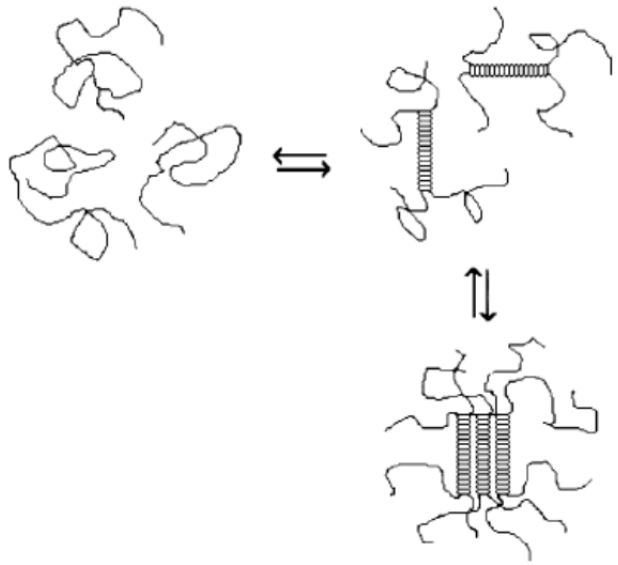

Figure 7: Gelation mechanism of polysaccharides in water (Guenet, 1992)

Table 8: Some applications of the ionic gelation technique

Encapsulated molecule	Polymer	Size (µm)	Zeta potential (mV)	Reference
Articaine hydrochloride	Alginate/chitosan	0.340-0.550	-22 - (-19)	de Melo et al., 2013
TNF-α siRNA	Trimethyl chitosan-cysteine	0.146	25.9	He et al., 2013
Paclitaxel	O-carboxymethyl chitosan	0.130-0.180	-30 - (-12)	Maya et al., 2013
pDNA	Chitosan	0.153-0.403	46.2-56.9	Cadete et al., 2012
Gemcitabine	Chitosan	0.095	-	Derakhshandeh and Fathi, 2012
Dexamthasone sodium phosphate	Chitosan	0.256-0.350	-	Doustgani et al., 2012
Itraconazole	Chitosan	0.190-0.240	11.5-18.9	Jafarinejad et al., 2012
5-fluorouracil and leucovorin	Chitosan	0.040-0.097	25.6-28.9	Li et al., 2011
Insulin	Chitosan and arabic gum	0.172-0.245	35.7-43.4	Avadi et al., 2010
CKS9 peptide sequence	Chitosan	0.226	-	Yoo et al., 2010

3.8 Layer by layer

Polyelectrolyte self assembly is also called layer-by-layer (LbL) assembly process. The earliest technology was based on the assembly of colloidal particles on a solid core (Iler, 1966). From the 1990s, applications were expanded. LbL allowed, in fact, the assembly of polyelectrolyte films using biopolymers, proteins, peptides, polysaccharides and DNA (Powell et al., 2011). This approach was first developed by Sukhorukov et al. (Sukhorukov et al., 1998). Polyelectrolytes are classified according to their origin. Standard synthetic polyelectrolytes include poly(styrene sulfonate) (PSS), poly (dimethyldiallylammonium chloride) (PDDA), poly(ethylenimine) (PEI), poly(N-isopropyl acrylamide (PNIPAM), poly-

(acrylic acid) (PAA), poly (methacrylic acid) (PMA), poly(vinyl sulfate) (PVS) and poly(allylamine) (PAH). Natural polyelectrolytes include nucleic acids, proteins and polysaccharides such as, alginic acid, chondroitin sulfate, DNA, heparin, chitosan, cellulose sulfate, dextran sulfate and carboxymethylcellulose (de Villiers et al., 2011). The obtained particles are vesicular and are called polyelectrolyte capsules. Assembly process is based on irreversible electrostatic attraction that leads to polyelectrolyte adsorption at supersaturating polyelectrolyte concentrations. Other interactions such as, hydrogen bonds, hydrophobic interactions and Van der Waals forces were also described (de Villiers et al., 2011). A colloidal template that serves to the adsorption of the polyelectrolyte is also needed. The commonly used cores for the formulated particles are derived from stabilized colloidal dispersions of charged silica, charged poly(styrene) spheres, metal oxides, polyoxometalates and conducting liquid crystalline polymers. Carrier systems can be functionalized with stimuli-responsive components that respond to temperature, pH and ionic strength. The polymers/colloids used in LbL technique can also be functionalized to alter their properties preceding layer by layer assembly. Experimental parameters that have to be managed include coating material concentration, ion concentration and the pH of the medium (Vergaro et al., 2011). Polymer assembly occurs after incubation of the template in the polymer solution or by decreasing polymer solubility by drop-wise addition of a miscible solvent (Radtchenko et al., 2002). This procedure could be repeated with a second polymer to allow sequential deposition of multiple polymer layers (Figure 8). LbL presents advantages over several conventional coating methods: (1) simplicity of the process and equipment; (2) its suitability for coating most surfaces; (3) availability and abundance of natural and synthetic colloids; (4) flexible application to objects with irregular shapes and sizes; (5) formation of stabilizing coats and (6) control over the required multilayer thickness (de Villiers et al., 2011). Table 9 contains some recent applications of LbL technique.

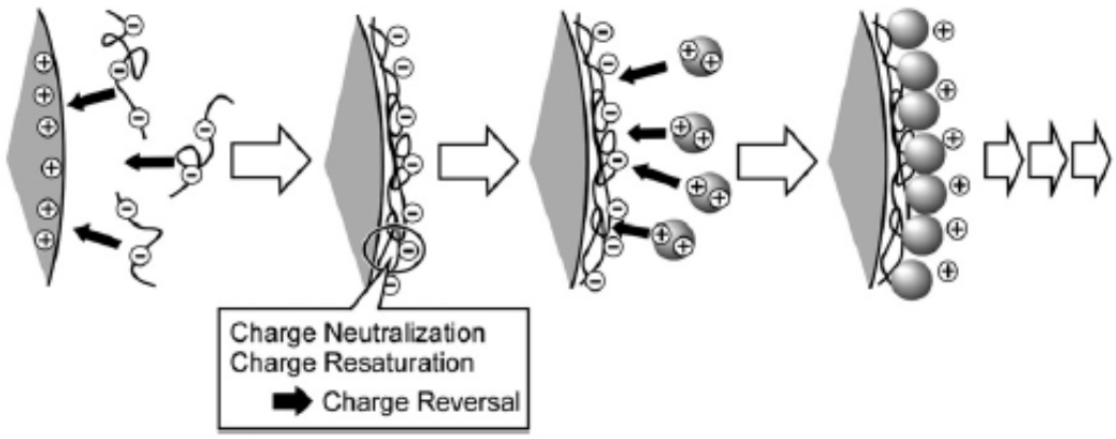

Figure 8: The layer by layer technique based on electrostatic interaction (Ariga et al., 2011)

Table 9: Applications of the layer-by-layer technique

Active	Polyelectrolytes	Size (µm)	Zeta potential (mV)	References
Kaempferol	Sodium Alginate and protamine sulfate	0.161	- 8.9	Kumar et al., 2012
Designed peptide DP-2015	Poly-l-glutamic acid and poly-l-lysine	-	-	Powell et al., 2011
5-fluorouracil	Poly(L-glutamic acid) and chitosan	1	25-40	Yan et al., 2011
Plasmid DNA	Plasmid DNA and reducible hyperbranched poly(amidoamine) or polyethylenimine	-	-	Blacklock et al., 2009
Artemisinin	Alginate, gelatin and chitosan	0.806	-33	Chen et al., 2009
Insulin	Glucose oxidase and catalase	6	-	Qi et al., 2009
Heparin	Poly(styrene sulfonate) and chitosan	1	-10.4	Shao et al., 2009
Acyclovir	Poly(vinyl galactose ester-co-methacryloxyethyl trimethylammonium chloride) and poly(sodium 4-styrenesulfonate)	-	-	Zhang et al., 2008a
Propranolol hydrochloride	Poly(vinyl galactose ester-*co*-methacryloxyethyl trimethylammonium chloride) and Poly(sodium 4-styrenesulfonate)	5-15.6	-	Zhang et al., 2008b

CONCLUSION

Encapsulation of active molecules is a crucial approach that has been widely used for many biomedical applications. It permits enhancement of bioavailability of molecules, sustained delivery, passive or active targeting and decrease of toxicity and side effects. These formulations can render some active molecules more suitable for a specific route such as the delivery of proteins by the oral route or the delivery of some drugs via the blood brain barrier. Thus, they enhance efficiency, patient compliance and allow successful management of diseases. Many biodegradable and biocompatible polymers were investigated. The choice of the technique and the suitable polymer is a crucial step. It depends on the physicochemical properties of the drug to be encapsulated. The management of operating conditions is also a hard task to monitor particles' properties and to enhance drug loading. Recent research works are focusing on active targeting by the coating the carriers by biomolecules that specifically recognize a well-defined cell receptor. One can also notice a shift for more 'intelligent' drug delivery systems. Responsive materials, for example, react to a specific physiological stimulus such as a variation of pH to release the encapsulated drug. Other thermo-sensitive materials deliver drugs at a specific temperature. It can be noted also that more attention is paid to safer methods that avoid the use of organic solvents (RESS) or to techniques that provide better reproducibility and easy scalability (microfluidics and membrane emulsification technology), which could be attractive for industrial processing.

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